

AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A compound consisting of ~~a total of 8-50~~ 12-50 nucleotides and/or nucleotide analogues, wherein said compound comprises a subsequence of at least 8 nucleotides or nucleotide analogues, said subsequence being located within ~~a sequence selected from the group consisting of SEQ ID NOS: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74 or 75.~~, and wherein at least one of said nucleotides in said sequence has been replaced by a corresponding nucleotide analog.

2. (Previously Presented) A compound of claim 1, which modulates the expression of ras selected from Ha-ras, Ki-ras or N-ras.

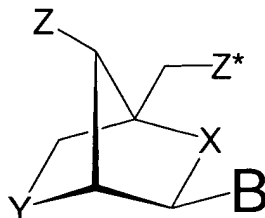
3. (Currently Amended) A compound consisting of ~~a total of 8-50~~ 12-50 nucleotides and/or nucleotide analogues targeted to a nucleic acid molecule encoding Ha-ras, wherein said compound specifically hybridises with a nucleic acid encoding Ha-ras and inhibits the expression of Ha-ras and wherein said compound comprises a subsequence of at least 8 nucleotides or nucleotide analogues, said subsequence being located within ~~a sequence selected from the group consisting of SEQ ID NO: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74 or 75.~~, and wherein at least one of said nucleotides in said sequence has been replaced by a corresponding nucleotide analog.

4. (Previously Presented) The compound according to claim 1, which is an antisense oligonucleotide.

5. (Canceled)

6. (Previously Presented) The compound according to claim 1, comprising at least one Locked Nucleic Acid (LNA) unit.

7. (Previously Presented) The compound according to claim 6, wherein the Locked Nucleic Acid (LNA) has the structure of the general formula

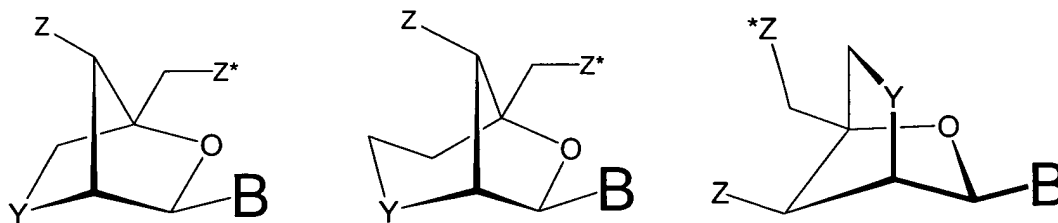


X and Y are independently selected among the groups -O-, -S-, -N(H)-, N(R)-, -CH₂- or -CH- (if part of a double bond), -CH₂-O-, -CH₂-S-, -CH₂-N(H)-, -CH₂-N(R)-, -CH₂-CH₂- or -CH₂-CH- (if part of a double bond), -CH=CH-, where R is selected from hydrogen and C₁₋₄-alkyl ; Z and Z* are independently absent, selected among an internucleoside linkage, a terminal group or a protecting group;

B constitutes a natural or non-natural nucleobase;

and the asymmetric groups may be found in either orientation.

8. (Original) The compound according to claim 6, wherein at least one nucleotide comprises a Locked Nucleic Acid (LNA) unit according any of the formulas



wherein Y is -O-, -S-, -NH-, or N(R^H); Z and Z* are independently absent, selected among an internucleoside linkage, a terminal group or a protecting group; and B constitutes a natural or non-natural nucleobase.

9. (Original) The compound according to claim 6 or 7, wherein the internucleoside linkage may be selected from the group consisting of -O-P(O)₂-O-, -O-P(O,S)-O-, -O-P(S)₂-O-, -S-P(O)₂-O-, -S-P(O,S)-O-, -S-P(S)₂-O-, -O-P(O)₂-S-, -O-P(O,S)-S-, -S-P(O)₂-S-, -O-PO(R^H)-O-, O-

$\text{PO}(\text{OCH}_3)\text{-O-}$, $\text{-O-PO}(\text{NR}^{\text{H}})\text{-O-}$, $\text{-O-PO}(\text{OCH}_2\text{CH}_2\text{S-R})\text{-O-}$, $\text{-O-PO}(\text{BH}_3)\text{-O-}$, $\text{-O-PO}(\text{NHR}^{\text{H}})\text{-O-}$, $\text{-O-P}(\text{O})_2\text{-NR}^{\text{H}}$, $\text{-NR}^{\text{H}}\text{-P}(\text{O})_2\text{-O-}$, $\text{-NR}^{\text{H}}\text{-CO-O-}$, where R^{H} is selected from hydrogen and C_{1-4} -alkyl.

10. (Original) The compound according to claim 5, 6 or 7, wherein the nucleobases is a modified nucleobases selected from the group consisting of 5-methylcytosine, isocytosine, pseudoisocytosine, 5-bromouracil, 5-propynyluracil, 6-aminopurine, 2-aminopurine, inosine, diaminopurine, 2-chloro-6-aminopurine.

11. (Original) The compound according to any of claims 6-8, wherein the LNA is oxy-LNA, thio-LNA, amino-LNA, in either the D- β or L- α configurations or combinations thereof.

12. (Canceled)

13. (Previously Presented) The compound according to claim 1, wherein the antisense oligonucleotide is a design according to any of the designs presented in Figure 1.

14. (Original) The compound according to claim 12, wherein the antisense oligonucleotide is a gapmer.

15. (currently amended) The compound according to claim 1, wherein the antisense oligonucleotide comprises 13, 14, 15, 16, 17, 18, 19, 20 or 21 nucleotides.

16. (Previously Presented) The compound according to claim 1, comprising 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 LNA units.

17. – 46. (Canceled)

47. (Previously Presented) A conjugate comprising the compound according to claim 1 and at least one non-nucleotide or non-polynucleotide moiety covalently attached to said compound.

48. (Previously Presented) A pharmaceutical composition comprising a compound as defined in claim 1 or a conjugate as defined in claim 47, and a pharmaceutically acceptable diluent, carrier or adjuvant.

49. (Previously Presented) The pharmaceutical composition according to claim 48 further comprising at least one chemotherapeutic agent.

50. (Original) The pharmaceutical composition according to claim 49, wherein said chemotherapeutic compound is selected from the group consisting of adrenocorticosteroids, such as prednisone, dexamethasone or decadron; altretamine (hexalen, hexamethylmelamine (HMM)); amifostine (ethyol); aminoglutethimide (cytadren); amsacrine (M-AMSA); anastrozole (arimidex); androgens, such as testosterone; asparaginase (elspar); bacillus calmette-gurin; bicalutamide (casodex); bleomycin (blenoxane); busulfan (myleran); carboplatin (paraplatin); carmustine (BCNU, BiCNU); chlorambucil (leukeran); chlorodeoxyadenosine (2-CDA, cladribine, leustatin); cisplatin (platinol); cytosine arabinoside (cytarabine); dacarbazine (DTIC); dactinomycin (actinomycin-D, cosmegen); daunorubicin (cerubidine); docetaxel (taxotere); doxorubicin (adriamycin); epirubicin; estramustine (emcyt); estrogens, such as diethylstilbestrol (DES); etoposide (VP-16, VePesid, etopophos); fludarabine (fludara); flutamide (eulexin); 5-FUDR (floxuridine); 5-fluorouracil (5-FU); gemcitabine (gemzar); goserelin (zodalex); herceptin (trastuzumab); hydroxyurea (hydrea); idarubicin (idamycin); ifosfamide; IL-2 (proleukin, aldesleukin); interferon alpha (intron A, roferon A); irinotecan (camptosar); leuprolide (lupron); levamisole (ergamisole); lomustine (CCNU); mechlorathamine (mustargen, nitrogen mustard); melphalan (alkeran); mercaptopurine (purinethol, 6-MP); methotrexate (mexate); mitomycin-C (mutamucin); mitoxantrone (novantrone); octreotide (sandostatin); pentostatin (2-deoxycoformycin, nipent); plicamycin (mithramycin, mithracin); prorocarbazine (matulane); streptozocin; tamoxifen (nolvadex); taxol (paclitaxel); teniposide (vumon, VM-26); thiotepa; topotecan (hycamtin); tretinoin (vesanoid, all-trans retinoic acid); vinblastine (valban); vincristine (oncovin) and vinorelbine (navelbine).

51. (Previously Presented) A pharmaceutical composition comprising the compound of claim 1, which further comprises a pharmaceutically acceptable carrier.

52. (Previously Presented) A pharmaceutical composition comprising the compound of claim 1, which is employed in a pharmaceutically acceptable salt.

53. (Previously Presented) A pharmaceutical composition comprising the compound of claim 1, which is constitutes a pro-drug.

54. (Previously Presented) A pharmaceutical composition comprising the compound of claim 1, which further comprises an anti-inflammatory compounds and/or antiviral compounds.

55. – 63. (Canceled)

64. (Withdrawn) A method for treating cancer, said method comprising administering a compound as defined in claim 1, a conjugate as defined in claim 47 or a pharmaceutical composition as defined in claim 48 to a patient in need thereof.

65. (Withdrawn) The method according to claim 64, wherein said cancer is in the form of a solid tumor.

66. (Withdrawn) The method according to claim 64, wherein said cancer is a carcinoma.

67. (Withdrawn) The method according to claim 66, wherein said carcinoma is selected from the group consisting of malignant melanoma, basal cell carcinoma, ovarian carcinoma, breast carcinoma, non-small cell lung cancer, renal cell carcinoma, bladder carcinoma, recurrent superficial bladder cancer, stomach carcinoma, prostatic carcinoma, pancreatic carcinoma, lung carcinoma, cervical carcinoma, cervical dysplasia, laryngeal papillomatosis, colon carcinoma, colorectal carcinoma and carcinoid tumors.

68. (Withdrawn) The method according to claim 67, wherein said carcinoma is selected from the group consisting of malignant melanoma, non-small cell lung cancer, breast carcinoma, colon carcinoma and renal cell carcinoma.

69. (Withdrawn) The method according to claim 68 wherein said malignant melanoma is selected from the group consisting of superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, acral melanoma, amelanotic melanoma and desmoplastic melanoma.

70. (Withdrawn) The method according to claim 64, wherein said cancer is a sarcoma.

71. (Withdrawn) The method according to claim 70, wherein said sarcoma is selected from the group consisting of osteosarcoma, Ewing's sarcoma, chondrosarcoma, malignant fibrous histiocytoma, fibrosarcoma, arteriosclerosis, psoriasis, diabetic retinopathy, rheumatoid arthritis, asthma, warts, allergic dermatitis and Kaposi's sarcoma.

72. (Withdrawn) The method according to claim 64, wherein said cancer is a glioma.

73. (Withdrawn) A method of inhibiting the expression of Ha-ras, in cells or tissues comprising contacting said cells or tissues with the compound according to claim 1 so that expression of Ha-ras is inhibited.

74. (Withdrawn, Currently Amended) A method of modulating expression of a gene involved in a cancer disease comprising contacting the gene or RNA from the gene with an oligomeric compound according to claim 1, ~~wherein said compound has a sequence comprising at least an 8 nucleobase portion of SEQ ID NO: 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74 or 75~~ whereby gene expression is modulated.

75. (Withdrawn, Currently Amended) A method according to claim 74, wherein the compounds comprises one or more LNA units.

76. (Withdrawn) The method of claim 74, wherein the compound hybridizes with messenger RNA of the gene to inhibit expression thereof.

77. (Canceled)

78. (Withdrawn, Currently Amended) The method according to any of the claims ~~74-77~~ 74-76, wherein the cancer diseases is a lung, breast, colon, prostate, pancreas, lung, liver, thyroid, kidney, brain, testes, stomach, intestine, bowel, spinal cord, sinuses, bladder, urinary tract or ovaries cancer.

79. (Withdrawn) A method of modulating the red blood cell proliferation, cellular proliferation, ion metabolism, glucose and energy metabolism, pH regulation or matrix metabolism comprising contacting a cell with the antisense compound of claim 1 so that the cell is modulated.

80. (Withdrawn) A method of inhibiting the proliferation of cells comprising contacting cells in vitro with an effective amount of the antisense-compound of claim 1, so that proliferation of the cells is inhibited.

81. (Withdrawn) The method of claim 80 wherein said cells are cancer cells.

82. (Withdrawn) A method of inhibiting the expression of Ha-ras in human cells or tissues comprising contacting human cells or tissues with the compound of claim 1 so that expression of Ha-ras is inhibited.

83. (Withdrawn) A method of treating an animal having a disease or condition associated with Ha-ras comprising administering to an animal having a disease or condition associated with Ha-ras a therapeutically or prophylactically effective amount of the antisense compound of claim 1 so that expression of Ha-ras is inhibited.

84. (Withdrawn) The method of claim 83 wherein the disease or condition is a hyperproliferative condition.

85. (Withdrawn) The method of claim 84 wherein the hyperproliferative condition is cancer.

86. (Withdrawn) A method of treating a human having a disease or condition characterized by a reduction in apoptosis comprising administering to a human having a disease or condition characterized by a reduction in apoptosis a prophylactically or therapeutically effective amount of the antisense compound of claim 1.

87. (Withdrawn) A method of modulating apoptosis in a cell comprising contacting a cell with the antisense compound of claim 1 so that apoptosis is modulated.

88. (Withdrawn) A method of modulating cytokinesis in a cell comprising contacting a cell with the antisense compound of claim 1 so that cytokinesis is modulated.

89. (Withdrawn) A method of modulating the cell cycle in a cell comprising contacting a cell with the antisense compound of claim 1 so that the cell cycle is modulated.

90. (Withdrawn) A method of inhibiting the proliferation of cells comprising contacting cells with an effective amount of the antisense compound of claim 1, so that proliferation of the cells is inhibited.